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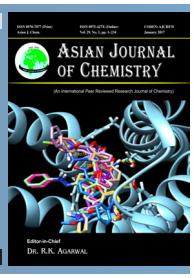

A Novel Synthesis and Characterization of 1,2,3,4-Tetrahydropyrimidin-2(1*H*)-thiones

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We reported the use of Brønsted acid methane sulfonic acid as a promoter for three component Biginelli cyclocondensation reaction of aryl aldehydes, acetylacetone and thiourea at 120 °C to afford the corresponding to 1,2,3,4-tetrahydropyrimidin-2(1*H*)-thiones in good to excellent yields in short span of time. Reaction is efficient, facile and rapid. The structural elucidation of products was done by NMR, IR and elemental analysis.

Keywords: Biginelli cyclocondensation, Acetylacetone, Arylaldehydes, Thiourea, Methanesufonic acid, 1,2,3,4-Tetrahydropyrimidithione.

INTRODUCTION

1,2,3,4-Tetrahydropyrimidinthione-2(1*H*)-thiones are heterocyclic compounds and non-planar. 1,2,3,4-Tetrahydropyrimidin-2(*1*H)-thiones (THPM) represents a remarkable pharmacologically efficient moieties and are with wide range of therapeutic properties [1]. These compounds have been the focus of much interest for both organic and medicinal chemistry areas. Moreover, 1,2,3,4-tetrahydropyrimidinthione motif is present in many products isolated in natural material such as several specifications of sponges [2]. Number of synthetic methods have been developed since Biginelli reaction is very important method for developing 1,2,3,4-tetrahydropyrimidinthione which are even part in some marine alkaloids. The three component Biginelli condensation gives many 1,2,3,4-tetrahydropyrimidinthione have been synthesized. And, many naturally occurring com-pounds and clinical useful molecule possess THPM moiety. The THPM have important the integral back bones of several calcium channels modulators and anti hypertensive agents, due to which Biginelli multi-component cyclo-condensation reaction received much attention. These derivatives show attractive biological effects such as antianalgesic [3]. Antibacterial [4], antifungal, antiinflammatory, antiproliferative, antiviral, antitumor, anti-tubercular, antihistamine, *etc*. Lewis acid catalysts like $Mn(OAc)_3{\cdot}2H_2O$ [5], $Cu(OTf)_2$ [6], VCl_3 [7], $Yb(OTf)_3$ and $LaCl_3{\cdot}7H_2O$ are known to catalyze this reaction. The polymer-supported, resin-bound isothiourea [8], poly(4-vinylpyridine-*co*-divinyl benzene–Cu^{2+}) complex ceria/vinyl-pyrimidine polymer nanocomposite [9], N-butyl-N,N-dimethyl-a-phenyl-ethyl ammonium bromide [10] were also reported.

Here, we report the Biginelli reaction promoted by Brønsted acid methanesulphonic acid. Methanesulphonic acid is an effective, low-cost, easily available and easily handled reagent for Biginelli-type condensation reaction for synthesis of 1,2,3,4-tetrahydropyrimidinthione.

EXPERIMENTAL

General procedure for synthesis of 3,4-dihydropyrimidin-thiones under methane sulfonic acid: Aromatic aldehydes (2.5 mmol), acetylacetone (2.5 mmol) and thiourea (3.0 mmol) were taken in methane sulponic acid and allowed to stir at 120 °C. The reaction was monitored by thin layer chromatography (TLC) (3:7 ethylacetate:hexane) and found to complete in 10-15 min. After completion of the reaction, mixture was cooled and washed with ice cooled water and then the resulting solid was filtered and dried in vacuum. The desired product was recrystallized from ethyl alcohol to afford the desired product 1,2,3,4-tetrahydropyrimidin-2-thione in pure form. The structural elucidation of products was done by NMR, IR and elemental analysis.

RESULTS AND DISCUSSION

Reaction of mixture of equimolar ratio of arylaldehyde, acetyl acetone and thiourea in methane sulfonic acid which has been considered as solvent and promoter for this cyclization condensation reaction resulted in 1,2,3,4-tetrahydropyrimidin-

2-thione in good yield (70 %) at room temperature and took 4 h for completion. At 120 °C, reaction was found to be very rapid as it completed in short span of time 10 min and resulting in good yield of 1,2,3,4-tetrahydropyrimidin-2-thione (92 %). Hence, further substrate scope was studied at 120 °C. All the reactions of arylaldehyde performed resulted in excellent yields and completed in 10-15 min. reaction has broad scope because of the easy availability of starting materials and importance of 1,2,3,4-tetrahydropyrimidin-2-thione derivatives.

Melting points of the products were measured using NR-VIS visual melting range apparatus and are uncorrected. IR spectra were recorded on a Shimadzu-IR Affinity. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer and 100 MHz respectively. NMR spectra were obtained in the solution using $CDCl_3$ as solvent using TMS as an internal standard. Elemental (C, H, N) analysis were done using FLASH EA analyzer. The method of preparation of all the five synthesized compounds are given below.

1-[4-{4-(Dimethylamino)phenyl}-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (Fig. 1): A mixture of N,N-dimethyl benzaldehyde (2.5 mmol), acetyl acetone (2.5 mmol) and thiourea (3 mmol) taken with methane sulphonic acid in round bottom and stirred the mixture on magnetic stirrer at 120 °C. The reaction was monitored by TLC. After completion of reaction taken with ethyl acetate and washed with $NaHCO_3$. The compound was recrystallized by ethanol. Yield 92 %, yellow colour compound, m.p. 237-239 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (br s. 1H), 7.45-7.75 (m, 2H), 6.69-6.71 (m, 2H), 5.21 (1H, d, *J* = 3.125, 1H), 3.05 (s, 6H), 2.36 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.6, 184.2, 144.4, 132.3, 130.1, 122.4, 122.0, 112.6, 111.9, 111.7, 111.0, 57.3, 40.1, 37.8, 29.7, 27.2. IR (KBr, ν_{max}, cm^{-1}): 3243, 3121, 2962, 1725, 1718, 1683, 1650, 1510, 1457, 1333, 1271, 769. Anal. calcd. for $C_{15}H_{19}N_3OS$: C, 62.25; H, 6.62; N, 14.52 %. Found: C, 61.87; H, 6.49; N, 14.70 %.

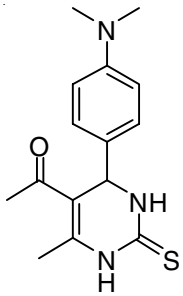

Fig. 1. 1-[4-{4-(Dimethylamino)phenyl}-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone

1-[4-(4-Methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (Fig. 2): A mixture of methoxy benzaldehyde (2.5 mmol), acetyl acetone (2.5 mmol) and thiourea (3 mmol) taken with methane sulphonic acid in round bottom and stirred on magnetic stirrer at 120 °C. The completion of the reaction was monitored by TLC. The compound taken with ethyl acetate and washed with $NaHCO_3$. The desired product obtained by recrystallization with ethonol. Yield 93 %, yellow colour compound, m.p. 182-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (br s, 1H), 7.45 (br s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 1H),

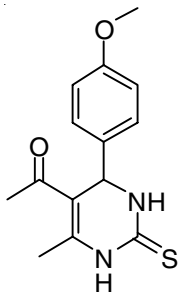

Fig. 2. 1-[4-(4-Methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone

3.80 (s, 3H), 2.37 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.5, 174.2, 159.8, 141.5, 133.8, 128.2, 114.8, 114.6, 111.6, 56.0, 55.3, 30.2, 19.4.IR (KBr, ν_{max}, cm^{-1}): Anal. calcd. for $C_{14}H_{16}N_2SO$: C, 60.8; H, 5.8; N, 10.1; S, 11.6. Found: C, 60.6; H, 6.0; N, 10.3; S, 11.5.

1-[6-Methyl-2-thioxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (Fig. 3): A mixture of 3,4,5-trimethoxy benzaldehyde (2.5 mmol), acetyl acetone (2.5 mmol) and thiourea (3 mmol) taken with methane sulphonic acid in round bottom and stirred on magnetic stirrer at 120 °C. The completion of the reaction was monitored by TLC. The compound taken with ethyl acetate and washed with $NaHCO_3$. The desired product obtained by recrystallization with ethonol. Yield 96 %, yellow colour compound, m.p. 152-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (br s, 2H), 6.68 (s, 1H), 6.48 (s, 1H), 5.09 (s, 1H), 3.96 (s, 6H), 3.90 (s, 3H), 2.70 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.4, 178.6, 153.7, 149.0, 142.0, 133.7, 115.6, 100.4, 60.8, 56.2, 45.6, 39.4, 30.8, 21.1. FT-IR (KBr, ν_{max}, cm^{-1}): 3298, 3001, 1615, 1591, 1568, 1187, 1124, 1019, 683. Anal. calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53. Found: C, 57.45; H, 5.98; N, 8.33; S, 10.44; MS (*m/z*: 336).

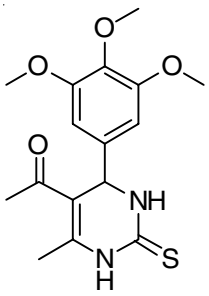

Fig. 3. 1-[6-Methyl-2-thioxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone

1-[4-(2-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (Fig. 4): A mixture of salicylaldehyde (2.5 mmol), acetyl acetone (2.5 mmol) and thiourea (3 mmol) taken with methane-sulphonic acid in round bottom and stirred on magnetic stirrer at 120 °C. The completion of the reaction was monitored by TLC. The compound taken with ethyl acetate and washed with $NaHCO_3$. The desired product obtained by recrystallization with ethonol. Yield 94 %, yellow colour compound, m.p.: 172-173 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (br s, 1H), 7.43 (br s, 1H), 7.15-7.06 (m, 4H), 4.70 (s, 1H), 3.03 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.0, 178.4, 153.6, 129.0, 127.4, 121.1,

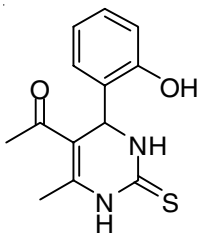

Fig. 4. 1-[4-(2-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone

117.1, 58.5, 31.2, 29.4, 24.4. Anal. calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.88; S, 12.22. Found: C, 60.83; H, 5.53; N, 10.72; S, 12.34; MS (*m/z*: 262). FT-IR (KBr, ν_{max}, cm^{-1}): 3229, 3146, 1609, 1588, 1195, 760, 719

1-[4-(3,4-Dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (Fig. 5): A mixture of 3,4-dimethoxy benzaldehyde (2.5 mmol), acetyl acetone (2.5 mmol) and thio urea (3 mmol) taken with methane sulphonic acid in round bottom and stirred on magnetic stirrer at 120 °C. The completion of the reaction was monitored by TLC. The compound taken with ethyl acetate and washed with $NaHCO_3$. The desired product obtained by recrystallization with ethonol. Yield 95 %, yellow colour compound, m.p. 220-221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (br s, 2H), 6.68-6.76 (m, 3H), 5.31 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.69 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.0, 174.3, 155.6, 153.4, 125.9, 114.5, 111.4, 107.2, 106.3, 103.8, 56.25, 56.19, 49.3, 22.3, 17.3. IR (KBr, ν_{max}, cm^{-1}): 3383, 3173, 2969, 1678, 1515, 1460, 1393 735.

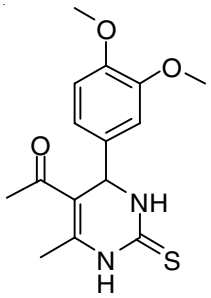

Fig. 5. 1-[4-(3,4-Dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone

REFERENCES

1. M. Abdollahi-Alibeik and Z. Zaghaghi, *Chem. Pap.*, **63**, 97 (2009); https://doi.org/10.2478/s11696-008-0084-1.
2. S. Chand, Suresh and S. Jagir Sandhu, *Rasayan J. Chem.*, **5**, 194 (2012).
3. R. Marchand, W. Schnick and N. Stock, *Adv. Inorg. Chem.*, **50**, 193 (2000); https://doi.org/10.1016/S0898-8838(00)50005-1.
4. V.L. Harika, K.R. Kumar and A.B. Shaik, *Arch. Appl. Sci. Res.*, **6**, 121 (2014).
5. B.B. Snider, *Tetrahedron*, **65**, 10738 (2009); https://doi.org/10.1016/j.tet.2009.09.025.
6. G. Sabitha, G.S. Kumar Reddy, K.B. Reddy and J.S. Yadav, *Synthesis*, 2298 (2003); https://doi.org/10.1055/s-2003-41070.
7. A.S. Paraskar, G.K. Dewkar and A. Sudalai, *Tetrahedron Lett.*, **44**, 3305 (2003); https://doi.org/10.1016/S0040-4039(03)00619-1.
8. M. Hirotsu, K. Nakajima, M. Kojima and Y. Yoshikawa, *Inorg. Chem.*, **34**, 6173 (1995); https://doi.org/10.1021/ic00128a031.
9. K.A. Kumar, M. Kasthuraiah, C.S. Reddy and C.D. Reddy, *Tetrahedron Lett.*, **42**, 7873 (2001); https://doi.org/10.1016/S0040-4039(01)01603-3.
10. G. Sabitha, K.B. Reddy, J.S. Yadav, D. Shailaja and K.S. Sivudu, *Tetrahedron Lett.*, **46**, 8221 (2005); https://doi.org/10.1016/j.tetlet.2005.09.100.